Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined perindopril 8 mg once daily, an angiotensin-converting enzyme inhibitor, for the prevention of cardiovascular events in patients with stable coronary artery disease. Treatment was assumed to last 5 years or until patient death. Perindopril was compared with placebo.

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a cohort of patients with stable coronary heart disease without apparent heart failure or hypertension (low-risk patients).

Setting
The setting was secondary care. The economic study was carried out in the UK.

Dates to which data relate
The clinical and economic data were derived from a study published in 2003. Most of the costs referred to 2003/04 prices. The exception was perindopril, the price of which related to January 2005.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the analysis of effectiveness.

Study sample
A sample of 12,218 patients was enrolled in the EUROPA trial. Other details of sample selection, number of patients included in the two treatment groups, and power calculations were not provided in the current publication. Some details were reported in the technical appendix. Overall, 85% of recruited patients were male and the mean age was 60 years.

Study design
This was a multi-centre, prospective, randomised, double-blind, placebo-controlled clinical trial. The number of institutions involved was not reported, but it was stated that the trial involved 24 countries in Europe. The mean length of follow-up was 4.2 years (maximum 5 years).
Analysis of effectiveness
The primary clinical measure was a combined end point of cardiovascular death, myocardial infarction (MI) and cardiac arrest. No details on methods of assessment (intention to treat or treatment completers only) or the comparability of the patients at baseline were reported in the current publication.

Effectiveness results
The rate of the combined end point fell from 9.9% in the placebo group to 8.0% in the perindopril group. This represented a relative risk of 0.80 (95% confidence interval, CI: 0.71 to 0.91) in favour of treatment.

Clinical conclusions
The effectiveness analysis showed that perindopril was an effective preventive treatment in comparison with placebo, as it reduced the risk of cardiovascular death, MI and cardiac arrest by 20%.

Modelling
A Markov model was constructed to project the analysis beyond the limited time horizon of the clinical trial that had a mean follow-up of 4.2 years. The transition rates and main health states were reported. The time horizon of the analysis was 50 years. Details of the model were presented in the online appendix in which the model structure was illustrated together with each parameter. The transition probabilities were based on risk equations that were accurately described. The main health states represented the risk of fatal and nonfatal cardiovascular events. Given the heterogeneity between the patients enrolled in the EUROPA study, the cost-effectiveness was estimated individually for each patient and the results presented for 5 typical patients: one of these patients represented the median cost-effectiveness of the population, two represented the interquartile range (IQR), and the final two represented the 2.5th and 97.5th centiles of cost-effectiveness.

Measure of benefits used in the economic analysis
The summary benefit measure used was the quality-adjusted life-years (QALYs). These were estimated using the modelling approach. The expected survival was combined with data on utility weights estimated from the second Welsh Health Survey, which collected SF-36 estimates from a general population survey. All patients in the EUROPA study were assigned an age- and gender-dependent utility score that was further reduced by the estimated disutility of having angina. The QALYs were discounted at an annual rate of 3.5%.

Direct costs
The viewpoint of the NHS was taken in the analysis. The analysis included the costs associated with perindopril, concomitant cardiac drugs, and inpatient stay (which was considered by specialty) due to cardiovascular events. The unit costs and the quantities of resources used were presented separately, and details were given in the technical appendix. Resource consumption was derived from the sample of patients included in the EUROPA study. The drug costs were estimated from the UK Department of Health Prescription Cost Analysis database. Hospitalisation costs were derived from UK Trust Financial Returns. Long-term costs were evaluated and an annual discount rate of 3.5% was applied. All costs were estimated for the period 2003 to 2004, except for those of perindopril, which reflected a price reduction in January 2005.

Statistical analysis of costs
The costs were estimated using regression analysis.

Indirect Costs
Productivity costs were not included.
Currency
UK pounds sterling (GBP).

Sensitivity analysis
A probabilistic sensitivity analysis was performed in order to address the issue of uncertainty in model parameters and variability in the patient population. Specifically, a Monte Carlo simulation was used to translate the precision in each input variable into a measure of uncertainty. The results of the analysis were presented for the 5 typical patients (5 indicative risk levels) using 95% CIs, and using cost-effectiveness acceptability curves that synthesised the probability that perindopril was cost-effective dependent on how much the NHS was willing to pay for an additional QALY. Alternative scenarios were also considered. These referred to the duration of treatment and treatment effect of perindopril subsequent to an initial primary event.

Estimated benefits used in the economic analysis
The median gain in QALY with perindopril over placebo was 0.049 (IQR: 0.054 to 0.031; 2.5th and 97.5th centiles: 0.104 and 0.016).

Cost results
The median additional cost associated with perindopril over placebo was 478 (IQR: 346 to 443; 2.5th and 97.5th centiles: 390 and 499).

Synthesis of costs and benefits
Incremental cost-utility ratios were calculated in order to combine the costs and benefits of the alternative strategies. The median incremental cost per QALY gained with perindopril over placebo was 9,700 (95% CI: 5,500 to 24,000). Perindopril was highly cost-effective in the patient at greatest risk of cardiovascular events (29% over 5 years, 2.5th percentile), with a cost per QALY of 3,700 (95% CI: 2,200 to 9,400). It was less cost-effective in patients at lowest risk (3% over 5 years, 97.5th percentile), with a cost per QALY of 31,195 (95% CI: 17,200 to 83,000).

The probabilistic sensitivity analysis showed that the probability that perindopril was cost-effective at a threshold of 30,000 per QALY was 0.99 (0.999 in a patient representing the 25th centile and 0.93 in a patient representing the 75th centile). At the threshold of 20,000, the probability was 0.94 (0.99 in a patient representing the 25th centile and 0.75 in a patient representing the 75th centile).

The scenario analysis suggested that the base-case results were robust to variations in the length of treatment and the protective effect of perindopril.

Authors' conclusions
Five years' perindopril in patients with stable coronary heart disease was very likely to be cost-effective in comparison with placebo.

CRD COMMENTARY - Selection of comparators
The choice of the interventions examined in the study was based on the comparison carried out in the EUROPA trial in which perindopril was compared with placebo. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The clinical data used in the analysis were derived from the EUROPA study. The use of a large, randomised clinical trial should have ensured a high internal validity, owing to the robust design. Thus, although little information on the
trial was presented in the current economic evaluation (as the study had already been published), the clinical estimates are likely to be valid. The multinational nature of the trial further enhances the representativeness of the patient population.

**Validity of estimate of measure of benefit**

The benefits (i.e. QALYs) were modelled. The source of the utility data used to calculate QALYs was explicitly reported. The authors noted that the fact that utility weights were obtained outside the EUROPA study might represent a limitation to the analysis. The benefits were discounted at the recommended rate. QALYs are an appropriate benefit measure as they capture the impact of the interventions on quality of life and survival, which are two relevant dimensions of health for patients with cardiovascular disease. Furthermore, QALYs can be compared with the benefits of other health care interventions.

**Validity of estimate of costs**

The analysis of the costs was consistent with the authors' stated perspective. A partial breakdown of cost items was presented. Extensive information on the unit costs and quantities of resources used was given, which enhances the possibility of replicating the analysis in other settings. The sources of all the costs were reported and were typical of the UK health care system. Resource consumption was carried out alongside the clinical trial. The reference prices for all categories of costs were given. Statistical analyses of the costs were performed using regression techniques.

**Other issues**

The authors reported the results from studies assessing the cost-effectiveness of other new preventive treatments for patients with cardiovascular disease. These suggested that contrasting results had been achieved, perhaps because of different dosages. The authors addressed the issue of the generalisability of the study results to other settings and stated that, although clinical data came from an international sample of patients, several aspects of the current economic evaluation reflected the UK setting. Thus, caution will be required if extrapolating these findings to other contexts. The issue of the heterogeneity in patients receiving the main intervention was the key element of the study and was adequately addressed by means of probabilistic sensitivity and sub-group analyses. The study results were not presented in detail in the main paper, the bulk of the information being provided in the appendix.

**Implications of the study**

The study results appear to support the use of perindopril for the prevention of cardiovascular events in patients with stable coronary disease.

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**Other publications of related interest**

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MeSH
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